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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	STANLEY, CHRISTOPHER J.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001 (original)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/313,385* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on September 22, 2003 has been entered. The claims pending in this application are claims 1 and 3-22. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on September 22, 2003.

Claim Objections

2. Claims 1 and 3 are objected to because of the following informality: "extending said primer to form an extended primer which replicates said template in complementary form" should be "extending said primer to form an extended primer which replicates from said template".

3. Claim 8 is objected to because of the following informality: "the action of polymerase incorporating nucleotides on to said primer" should be "the action of a polymerase wherein the polymerase incorporates nucleotides into said primer".

4. Claim 7 is objected to because of the following informality: "on of the two vinyl groups" should be "one of the two vinyl groups" in order to correspond to claim 7 filed on February 13, 2003.

5. Claim 9 is objected to because of the following informality: "(3sr" should be "(ssr)".

6. Claim 10 is objected to because of the following informalities: (1) "single stranded form" should be "a single stranded form"; and (2) "a first one of the template stranded" should be "one of the template strand".

7. Claim 22 is objected to because of the following informality: "utilizing a primer or a hybridization probe" should be " utilizing said primer or said hybridization probe".

8. Claim 20 is objected to because of the following informality: in order to better define said extend primer, examiner suggests that applicant changes the phrase "said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" to "said extended primer that has a sequence complementary to said sequence to be detected and is bound to said carrier macromolecule".

Appropriate correction is required.

Response to Arguments

In page 7, last paragraph of applicant's remarks, applicant indicates that "'[T]he examiner suggested amending this phrase in claim 20 to "said extended primer has sequence complementary to said sequence to be detected and is bound to said carrier macromolecule." The applicant has amended claim 20 as suggested by the examiner and is grateful for all of the suggested amendments to the objected claims as discussed above.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the objection because, in view of amended claim 20, applicant does not amend claim 20 as suggested by the examiner in previous office action.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 7 is rejected as vague and indefinite in view of the phrase "each of which moieties is attached to each of the carrier macromolecule and the primer by a covalent linkage formed between on of the two vinyl groups of a divinyl sulphone molecule and a reactive functionality on the carrier macromolecule or primer.". According to the first part of the phrase, it appears that both carrier macromolecule and primer contain one or more moieties from divinyl sulphone. However, the second part of the phrase indicates that one of carrier macromolecule and primer contains one or more moieties from divinyl sulphone. The first part and the second part of the phrase do not correspond each other. Please clarify.

12. Claim 8 recites the limitation "the action of polymerase incorporating nucleotides on to said primer" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no polymerase in claims 3-7. Please clarify.

13. Claim 13 recites the limitation "a second primer" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no second primer in claims 1-8. Please clarify.

14. Claim 14 is rejected as vague and indefinite because it is unclear whether another primer recited in claim 14 and at least another primer recited in claim 10 are identical or not. If another primer recited in claim 14 and at least another primer recited in claim 10 are identical, "another primer" in claim 14 should be "the another primer". Please clarify.

15. Claim 15 is rejected as vague and indefinite because it is unclear whether said primer recited in claim 15 is another primer recited in claim 14 or at least another primer recited in claim 10 or the primer recited in claim 1. Please clarify.

16. Claim 16 is rejected as vague and indefinite because it is unclear whether the primer recited in claim 16 is the primer recited in claim 15 or another primer recited in claim 14 or at least another primer recited in claim 10 or the primer recited in claim 1. Please clarify.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Houtz (US Patent No. 5,908,972, filed on July 29, 1996).

The invention is directed to a method of detecting the presence of a nucleic acid bound to a carrier macromolecule. Claim 18 requires that a first nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons contacts a second nucleic

acid having a carrier macromolecule having a molecular weight in excess of 80,000 Daltons under hybridization conditions and detects hybridization between said first and second nucleic acids.

Houtz teaches isolated spinach ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit/epsilon N-methyltransferase. As shown in Figure 5, an aliquot of 20 μg of spinach genomic DNA was digested with ScaI and EcoRI respectively, electrophoresed on a 0.7% agarose gel and processed for DNA Southern blot analysis by hybridization to a labeled rbcMT-S cDNA probe I (see figure legend of Figure 5 in columns 5 and 6, and column 13) wherein rbcMT-S cDNA probe I was 1056 bp (see lines 19-27 in column 11). Probe I detected a predicted major 2424-bp EcoRI fragment and three ScaI fragments including a 876-bp fragment (see lines 47-52 in column 13 and lines 1-7 of column 14) wherein Figure 5 showed a hybridization pattern of the Southern blot.

Regarding claim 18, since it is known in the art that a base of a single stranded DNA molecule is 325 Daltons (see attachment in previous office action) and hybridization probe and hybridization nucleic target become single strand before they hybridize each other in a hybridization assay, molecular weights of 1056 bp single stranded rbcMT-S cDNA probe I and 2424-bp single stranded EcoRI fragment detected by the hybridization assay are 343,200 Daltons and 787,800 Daltons respectively (in excess of 80,000 Daltons). Since 1056 bp single stranded rbcMT-S cDNA probe I hybridizes with a 2424-bp fragment in EcoR I digested spinach genomic DNAs, the single stranded rbcMT-S cDNA probe I contains first nucleic acid and a 2424-bp single stranded EcoR I fragment detected by the hybridization assay contains second nucleic acid

as recited in claim 18. Since a nucleic acid can be a carrier macromolecule and the content of the claim does not require that a carrier macromolecule is a non-nucleotide as recited in preamble of the claim, the single stranded rbcMT-S cDNA probe I (1056 bp) comprises a 528 bp first nucleic acid bound to a 528 bp a carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., 171,600 Daltons) and a 2424-bp single stranded EcoR I fragment detected by the hybridization assay comprises a 1212 bp second nucleic acid bound to a 1212 bp a carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., 393,900 Daltons) as recited in claim 18.

Therefore, Houtz teaches all limitations recited in claim 18.

Response to Arguments

In page 11, last paragraph bridging to page 12, first paragraph of applicant's remarks, applicant argues that Houtz does not teach claimed invention since this reference does not use a non-nucleotide carrier macromolecule.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection since content of the claim does not require a non-nucleotide carrier macromolecule.

19. Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by McCormick *et al.*, (Promega Notes Magazine Number 40, 1993, p.04).

The invention is directed to an immobilized nucleic acid. Claim 21 requires that an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide

carrier macromolecule having a molecular weight in excess of 80,000 Daltons wherein the macromolecule is bound to a solid support.

Regarding claim 21, McCormick *et al.,* teach to hybridize an oligonucleotide labeled with alkaline phosphatase with nucleic acids immobilized on a membrane (see Figure 2). Since alkaline phosphatase is directly and covalently attached to the oligonucleotide (see first page) and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, after the hybridization, alkaline phosphatase (ie., a non-nucleotide carrier macromolecule) is indirectly bound to the membrane (ie., a solid support) by the oligonucleotide.

Therefore, McCormick *et al.,* teach all limitations recited in claim 21.

20. Claims 1 and 3-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Dale *et al.,* (US Patent No. 5,856,092, filed on April 1995).

Dale *et al.,* teach detection of a nucleic acid sequence or a change therein.

Regarding claims 1, 3, and 5, Dale *et al.,* teach a method for detecting whether a specific nucleotide or base is at a particular position in a specific polynucleotide sequence. The method comprises: a) exposing, under hybridizing conditions, said specific polynucleotide sequence to an oligonucleotide primer wherein said primer has a sequence complementary to part of the specific polynucleotide sequence wherein said primer has incorporated at its 5' end an element selected from the group consisting of a separation element and a detectable element, and wherein said primer hybridizes at a location selected from the group consisting of (I) immediately adjacent to the particular position and (ii) not immediately adjacent to the particular position whereby there is

an intervening sequence between the particular position and primer bound to the specific polynucleotide sequence; b) extending said hybridized primer up to and including said specific nucleotide or base wherein the 3' terminal nucleotide is a ddNTP and further includes an element selected from the group consisting of a separation element and a detectable element with the proviso that said extended primer has at least one separation element and at least one detectable element; c) separating the product of step b) into fractions wherein one said fraction contains the primer extension product that contains the chain terminating nucleotide at said particular position; and d) determining whether said primer extension product having said chain terminating nucleotide at said particular position is present in said fraction by assaying said fraction wherein the assay does not include a digestion step wherein said separating step comprises contacting any extended primer with a molecule having affinity for the separation element, said molecule being linked to a support (ie., cellulose or agarose) that facilitates said separating; and separating said contacted extended primer to provide said fraction (see lines 50-53 in column 16, claims 1 and 2 in column 39 and Figure 1). Since Dale *et al.,* teach a primer bound to a cellulose and it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose), a cellulose has a molecular weight of 540,600 Daltons or more as recited in claim 5. Therefore, Dale *et al.,* disclose providing said primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., a cellulose) wherein said carrier macromolecule is a natural or synthetic polysaccharide or a cellulose derivative as recited in claims 1 and 3. Since Dale *et al.,* teach exposing, under hybridizing

conditions, said specific polynucleotide sequence to an oligonucleotide primer wherein said primer has a sequence complementary to part of the specific polynucleotide sequence and extending said hybridized primer up to and including said specific nucleotide or base (see claim 1 in column 39, Dale *et al.,* disclose hybridizing the bound primer to said template and extending said primer to form an extended primer which replicates from said template as recited in claims 1 and 3.

Regarding claims 4 and 6, since Dale *et al.,* teach that the support bound to the primer can be agarose (see lines 50-53 in column 16) and it is known that agarose is a natural polysaccharide with a molecular weight of about 120, 000 and can be dissolved in boiled water (see an attachment for agar), agarose taught by Dale *et al.,* is a carrier macromolecular as recited in claim 6. Since it is known that agarose is a linear polymer and can be used in gel electrophoresis at least at pH from 7 to 8 without altering its properties, claim 4 is anticipated by Dale *et al.*.

Therefore, Dale *et al.*, teach all limitations recited in claims 1 and 3-6.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick *et al.,*(US Patent No.4,760,017, published on July 26, 1988) in view of Yamane *et al.,* (US Patent No.4,876,335, published on October 24, 1989).

The invention is directed to an immobilized nucleic acid and a method of using the immobilized nucleic acid. Claim 21 requires that an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons wherein the macromolecule is bound to a solid support. Claim 22 requires to formulate the immobilized nucleic acid recited in claim 21 as a primer or as a hybridization probe and introduce the immobilized nucleic acid into a hybridization or amplification reaction.

McCormick *et al.,* teach to hybridize a target nucleic acid to a single stranded nucleic acid immobilized on a support (see column 3).

McCormick *et al.,* do not disclose an immobilized nucleic acid as recited in claim 21 and using the immobilized nucleic acid as recited in claim 21 for hybridization.

Yamane *et al.,* teach to use a polylysine-labeled oligonucleotide for hybridization (see abstract). Lysine residues on the polylysine can be any desired numbers wherein the polylysine is covalently connected to the oligonucleotide (see column 2).

Regarding claims 21 and 22, since lysine resides on the polylysine of the oligonucleotide taught by Yamane *et al.,* can be any desired numbers, molecular weight of polylysine on the oligonucleotide can be in excess of 80,000 Dalton. It is known that polylysine with a molecular weight in excess of 80,000 Dalton is commercially available at the time the invention was made.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., polylysine) as recited in claim 21 wherein the macromolecule is bound to a solid support and used the immobilized nucleic acid as recited in claim 21 as a hybridization probe in view of the patents of McCormick *et al.,* and Yamane *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind nucleic acid probe (ie., an immobilized single stranded nucleic acid taught by McCormick *et al.,*) from another kind nucleic acid probe (i.e., a polylysine-labeled oligonucleotide taught by Yamane *et al.,*) during the process for making and using the immobilized nucleic acid probe recited in claims 21 and 22 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would enhance the hybridization between the target nucleic acid and the immobilized single stranded nucleic acid probe since polylysine-labeled oligonucleotide taught by Yamane *et al.,*carries positive charges.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. No claim is allowed.

25. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG

94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion , can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
PSA
December 29, 2003

BJ FORMAN, PH.D.
PRIMARY EXAMINER